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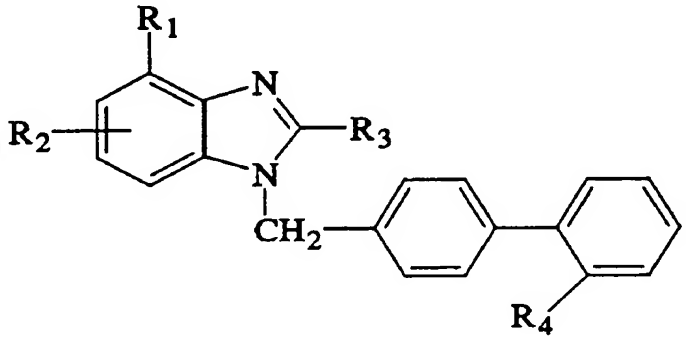
(54) **BENZIMIDAZOLES; COMPOSITIONS PHARMACEUTIQUES CONTENANT CES PRODUITS ET METHODES DE PREPARATION**

(54) **BENZIMIDAZOLES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS AND PROCESSES FOR PREPARING THEM**



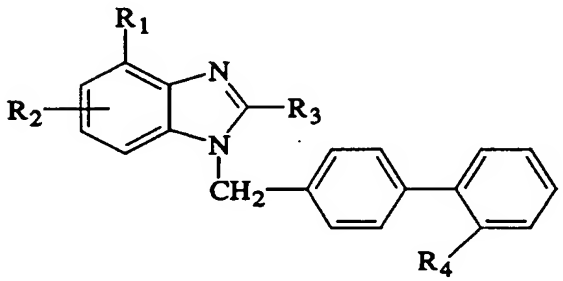
(I)

(57) The invention relates to compounds of formula I (see above formula) and addition salts thereof. As examples of groups R_1, there are mentioned fluorine, chlorine, bromine, alkyl and cycloalkyl and as examples of groups R_2 there are mentioned alkyleneimino, alkenyleneimino, malefic acid imido, benzimidazol-2-yl and 4,5,6,7-tetrahydrobenzimidazol-2-yl. R_3 represents an alkyl or a cycloalkyl group and R_4 represents a carboxyl or 1H-tetrazolyl group. The new compounds have useful pharmaceutical properties and are, in particular, angiotensin antagonists.

ABSTRACT

Benzimidizole Compounds

The invention relates to compounds of formula I



(I) ,

and addition salts thereof. As examples of groups R_1, there are mentioned fluorine, chlorine, bromine, alkyl and cycloalkyl and as examples of groups R_2 there are mentioned alkyleneimino, alkenyleneimino, maleic acid imido, benzimidazol-2-yl and 4,5,6,7-tetrahydrobenzimidazol-2-yl. R_3 represents an alkyl or a cycloalkyl group and R_4 represents a carboxyl or 1H-tetrazolyl group. The new compounds have useful pharmaceutical properties and are, in particular, angiotensin antagonists.

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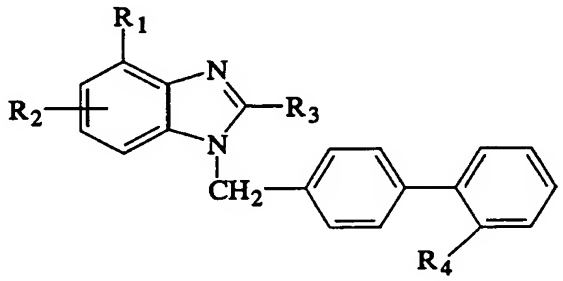
The present invention is concerned with benzimidazole compounds, the isomers and salts thereof, which are useful pharmaceutically and especially as angiotensin antagonists.

The new benzimidazoles of the present invention are suitable for the treatment of hypertension and cardiac insufficiency and also for treating ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), for the prevention of the progression of cardiac insufficiency after myocardial infarction and for treating diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases.

EP-A-0 392 317 has already described benzimidazoles which are valuable as angiotensin antagonists.

It has now been found that the new benzimidazoles of general formula



(I),

which differ from the benzimidazoles described in the above-mentioned published applications by the group R_2, and the compounds of general formula I wherein R_2 denotes a pyridyl or imidazolyl group, constitute a selection from EP-A-0,400,835,

are even more useful angiotensin-II antagonists than those known from the literature.

The present invention thus relates to the new benzimidazoles of the above general formula I and the salts thereof, particularly, for pharmaceutical use, the physiologically acceptable salts thereof with inorganic or organic acids, pharmaceutical compositions containing these compounds and processes for preparing them.

In general formula I above:

R_1 represents a fluorine, chlorine or bromine atom, an alkyl, cycloalkyl, fluoromethyl, difluoromethyl or

trifluoromethyl group and

R_2 represents a 5-, 6- or 7-membered alkyleneimino or alkenyleneimino group, optionally substituted by one or two alkyl groups or by a tetramethylene or pentamethylene group, wherein a methylene group may be replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by an alkyl or phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by C_{1-6}-alkyl or a cycloalkyl group, whilst the phenyl nucleus of one of the abovementioned benzimidazole groups may additionally be substituted by a fluorine atom or by a methyl or trifluoromethyl group, R_2 may represent an imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]-pyridazin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group,

a pyridyl group or

a carbon attached imidazolyl group optionally substituted in the 1-position by an alkyl or benzyl group, and which may also be substituted in the carbon skeleton by an alkyl group,

R_3 represents a C_{1-5}-alkyl group or a C_{3-5}-cycloalkyl group and

R_4 represents a carboxy or 1H-tetrazolyl group,

whilst, unless otherwise specified, an alkyl moiety mentioned hereinbefore may contain 1 to 3 carbon atoms in each case and a cycloalkyl moiety mentioned hereinbefore may contain 3 to 7 carbon atoms in each case.

As examples of the definitions of the groups R_1 to R_3 mentioned hereinbefore:

R_1 may represent a fluorine, chlorine or bromine atom, a methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, fluoromethyl, difluoromethyl or trifluoromethyl group,

R_2 may represent a 2-oxo-pyrrolidino, 2-oxo-piperidino, 2-oxo-hexamethyleneimino, propanesultam-1-yl, butanesultam-1-yl, pentanesultam-1-yl, maleic acid imido, 2-methyl-maleic acid imido, 2-phenyl-maleic acid imido, 2-methyl-3-phenyl-maleic acid imido, pyridin-2-yl, 4-methyl-imidazol-2-yl, 1-methyl-imidazol-4-yl, 1-methyl-imidazol-5-yl, 1-benzyl-imidazol-4-yl, 1-benzyl-imidazol-5-yl, 1,2-dimethyl-imidazol-4-yl, 1,2-dimethyl-imidazol-5-yl, 1-benzyl-2-methyl-imidazol-4-yl, 1-benzyl-2-methyl-imidazol-5-yl, benzimidazol-2-yl, 1-methyl-benzimidazol-2-yl, 1-ethyl-benzimidazol-2-yl, 1-n-propyl-benzimidazol-2-yl, 1-isopropyl-benzimidazol-2-yl, 1-n-butyl-benzimidazol-2-yl, 1-isobutyl-benzimidazol-2-yl, 1-n-pentyl-benzimidazol-2-yl, 1-n-hexyl-benzimidazol-2-yl, 1-cyclopropyl-benzimidazol-2-yl, 1-cyclobutyl-benzimidazol-2-yl, 1-cyclopentyl-benzimidazol-2-yl, 1-cyclohexyl-benzimidazol-2-yl, 5-methyl-benzimidazol-2-yl, 1,5-dimethyl-benzimidazol-2-yl, 1,6-dimethyl-benzimidazol-2-yl, 1,4-dimethyl-benzimidazol-2-yl, 5-fluoro-1-methyl-benzimidazol-2-yl, 6-fluoro-1-methyl-benzimidazol-2-yl, 5-trifluoromethyl-

benzimidazol-2-yl, 5-trifluoromethyl-1-methyl-benzimidazol-2-yl, 4,5,6,7-tetrahydro-benzimidazol-2-yl, 4,5,6,7-tetrahydro-1-methyl-benzimidazol-2-yl, 4,5,6,7-tetrahydro-1-ethyl-benzimidazol-2-yl, 4,5,6,7-tetrahydro-1-n-butyl-benzimidazol-2-yl, 4,5,6,7-tetrahydro-1-n-hexyl-benzimidazol-2-yl, 4,5,6,7-tetrahydro-1-cyclopropyl-benzimidazol-2-yl, 4,5,6,7-tetrahydro-1-cyclohexyl-benzimidazol-2-yl, imidazo-[1,2-a]pyrimidin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo-[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group and

R_3 may represent a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.butyl, n-pentyl, 1-methyl-butyl, 2-methyl-butyl, 3-methyl-butyl, cyclopropyl, cyclobutyl or cyclopentyl group.

Preferred compounds of general formula I above are those wherein

R_1 represents a chlorine atom, or a C_{1-3}-alkyl or a trifluoromethyl group,

R_2 represents a 5-, 6- or 7-membered alkyleneimino group wherein a methylene group is replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by a C_{1-3}-alkyl or phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by a

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C_{1-6}-alkyl or by a cycloalkyl group, whilst the phenyl nucleus of one of the abovementioned benzimidazole groups may additionally be substituted by a fluorine atom or by a methyl or trifluoromethyl group, or R_2 may represent an imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]-pyridazin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group,

a pyridyl group or

an imidazol-4-yl group substituted in the 1-position by a C_{1-3} alkyl group or by a benzyl group which may also be substituted in the carbon skeleton by a C_{1-3} alkyl group,

R_3 represents a C_{1-5}-alkyl group or a C_{3-5}-cycloalkyl group and

R_4 represents a carboxy or 1H-tetrazolyl group,

and the salts thereof with inorganic or organic acids or bases.

Particularly preferred compounds of general formula I above are those wherein

R_1 represents a methyl group or a chlorine atom and

R_2 represents a 5-, 6- or 7-membered alkyleneimino group, wherein a methylene group is replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or

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disubstituted by a C_{1-3}-alkyl or phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by a C_{1-3}-alkyl group, whilst the phenyl nucleus of one of the abovementioned benzimidazole groups may additionally be substituted by a fluorine atom, or R_2 may represent an imidazo[1,2-a]-pyridin-2-yl group, 5,6,7,8-tetrahydro-imidazo[1,2-a]-pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl or imidazo[2,1-b]thiazol-6-yl group,

an imidazol-4-yl group substituted in the 1-position by a C_{1-3} alkyl group,

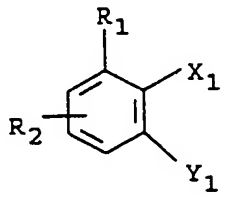
R_3 represents a C_{1-5}-alkyl group or a C_{3-5}-cycloalkyl group and

R_4 represents a carboxy or 1H-tetrazolyl group,

and the salts thereof with inorganic or organic acids or bases.

According to the invention, the compounds are obtained by the following processes:

a) Cyclising a compound of general formula



(II),

wherein
R_1 and R_2 are defined as hereinbefore,

one of the groups X_1 or Y_1 represents a group of general formula

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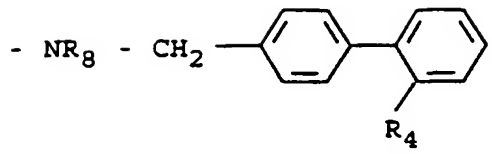
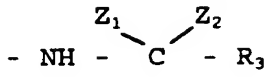
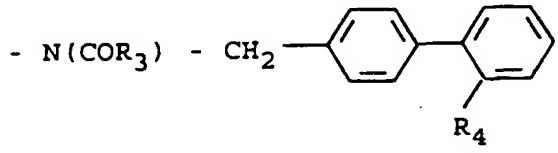


and the other group X_1 or Y_1 represents a group of the general formula

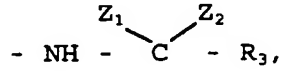


wherein

R_3 and R_4 are defined as hereinbefore,
R_8 represents a hydrogen atom or an R_3CO- group, wherein R_3 is defined as hereinbefore,
Z_1 and Z_2, which may be identical or different, represent optionally substituted amino groups or hydroxy or mercapto groups optionally substituted by lower alkyl groups or
Z_1 and Z_2, together represent an oxygen or sulphur atom, an optionally C_{1-3}-alkyl substituted imino group, or a C_{2-3}-alkylenedioxy or C_{2-3}-alkylenedithio group,
but one of the groups X_1 or Y_1 must represent a group of general formula



or



optionally with reduction of the corresponding N-oxide

thus obtained.

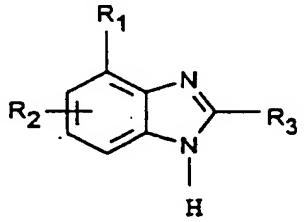
The cyclisation is conveniently carried out in a solvent or mixture of solvents such as ethanol, isopropanol, glacial acetic acid, benzene, chlorobenzene, toluene, xylene, glycol, glycolmonomethylether, diethyleneglycol-dimethylether, sulpholane, dimethylformamide, tetraline or in an excess of the acylating agent used to prepare the compound of general formula II, e.g. in the corresponding nitrile, anhydride, acid halide, ester or amide, e.g. at temperatures between 0 and 250°C, but preferably at the boiling temperature of the reaction mixture, optionally in the presence of a condensing agent such as phosphorusoxychloride, thionylchloride, sulphurylchloride, sulphuric acid, p-toluenesulphonic acid, methanesulphonic acid, hydrochloric acid, phosphoric acid, polyphosphoric acid, acetic anhydride or optionally in the presence of a base such as potassium ethoxide or potassium tert.-butoxide. However, cyclisation may also be carried out without a solvent and/or condensing agent.

However, it is particularly advantageous to carry out the reaction by preparing a compound of general formula II in the reaction mixture by reducing a corresponding o-nitro-amino compound, optionally in the presence of a carboxylic acid of general formula R_3COOH, or by acylation of a corresponding o-diamino compound. When the reduction of the nitro group is broken off at the hydroxylamine stage, the N-oxide of a compound of general formula I is obtained in the subsequent cyclisation. The resulting N-oxide is then converted by reduction into a corresponding compound of general formula I.

The subsequent reduction of the N-oxide of formula I obtained is preferably carried out in a solvent such as

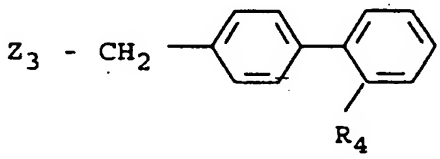
water, water/ethanol, methanol, glacial acetic acid, ethyl acetate or dimethylformamide with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid such as acetic, hydrochloric or sulphuric acid, with salts such as iron(II)sulphate, tin(II)chloride or sodium dithionite, or with hydrazine in the presence of Raney nickel at temperatures between 0 and 50°C, but preferably at ambient temperature.

b) Reaction of a benzimidazole of general formula



(III),

wherein
R_1 to R_3 are defined as hereinbefore, with a biphenyl compound of general formula



(IV),

wherein
R_4 is defined as hereinbefore and
Z_3 represents a nucleophilic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom, or a substituted sulphonyloxy group, e.g. a methanesulphonyloxy, phenylsulphonyloxy or p-toluenesulphonyloxy group.

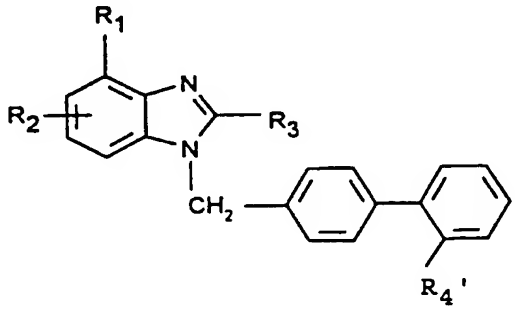
The reaction is conveniently carried out in a solvent or mixture of solvents such as methylene chloride,

diethylether, tetrahydrofuran, dioxane, dimethyl-sulphoxide, dimethylformamide or benzene, optionally in the presence of an acid binding agent such as sodium carbonate, potassium carbonate, sodium hydroxide, potassium tert.-butoxide, triethylamine or pyridine, whilst the latter two may simultaneously also be used as solvent, preferably at temperatures between 0 and 100°C, e.g. at temperatures between ambient temperature and 50°C.

In the reaction, a mixture of the 1- and 3- isomers is preferably obtained which can if desired subsequently be resolved into the corresponding 1- and 3- isomers, preferably by chromatography using a substrate such as silica gel or aluminium oxide.

c) In order to prepare a compound of general formula I wherein R_4 represents a carboxy group:

Converting a compound of general formula



(V),

wherein
R_1 to R_3 are defined as hereinbefore and
R_4' represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis.

For example, functional derivatives of the carboxy group such as unsubstituted or substituted amides, esters,

thiolesters, orthoesters, iminoethers, amidines or anhydrides, a nitrile group or a tetrazolyl group may be converted into a carboxy group by hydrolysis, esters with tertiary alcohols, e.g. tert.butylester, may be converted into a carboxy group by thermolysis and esters with aralkanols, e.g. benzylester, may be converted into a carboxy group by hydrogenolysis.

The hydrolysis is conveniently carried out in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trichloroacetic or trifluoroacetic acid in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxane at temperatures between -10°C and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture. When hydrolysis is carried out in the presence of an organic acid such as trichloroacetic or trifluoroacetic acid, any alcoholic hydroxy groups present may optionally be simultaneously converted into a corresponding acyloxy group such as a trifluoroacetoxy group.

If R_4' in a compound of general formula V represents a cyano or aminocarbonyl group, these groups may also be converted into a carboxy group with a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, which may also be simultaneously used as solvent, at temperatures between 0 and 50°C.

If R_4' in a compound of general formula V represents, for example, a tert.-butyloxycarbonyl group, the tert.-butyl group may also be thermally cleaved, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an

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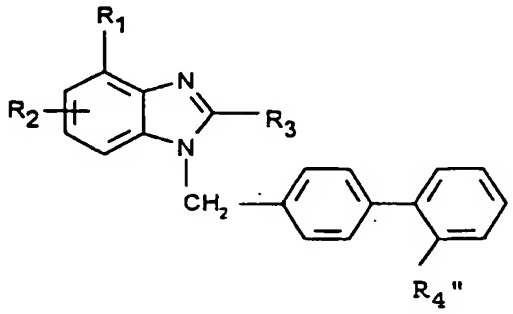
acid such as p-toluenesulphonic acid, sulphuric, phosphoric or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40°C and 100°C.

If R_4' in a compound of general formula V represents, for example, a benzyloxycarbonyl group, the benzyl group may also be hydrogenolytically cleaved in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at ambient temperature, under a hydrogen pressure of 1 to 5 bar. During hydrogenolysis, other groups may be reduced at the same time, e.g. a nitro group may be reduced to an amino group, a benzyloxy group to a hydroxy group, a vinylidene group to the corresponding alkylidene group or a cinnamic acid group to the corresponding phenyl-propionic acid group, or they may be replaced by hydrogen atoms, e.g. a halogen may be replaced by a hydrogen atom.

d) In order to prepare a compound of general formula I wherein R_4 represents a 1H-tetrazolyl group:

Cleaving of a protective group from a compound of general formula



(VI),

wherein

R_1, R_2 and R_3 are defined as hereinbefore and

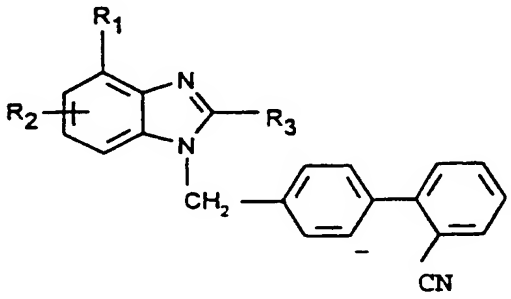
R_4" represents a 1H-tetrazolyl group protected in the 1- or 3-position by a protecting group.

Suitable protecting groups include, for example, triphenylmethyl, tributyl tin or triphenyl tin groups.

The cleaving of a protective group used is preferably carried out in the presence of a hydrohalic acid, preferably in the presence of hydrochloric acid, in the presence of a base such as sodium hydroxide or alcoholic ammonia, in a suitable solvent such as methylene chloride, methanol, methanol/ammonia, ethanol or isopropanol at temperatures between 0 and 100°C, but preferably at ambient temperature or, if the reaction is carried out in the presence of alcoholic ammonia, at elevated temperatures, e.g. at temperatures between 100 and 150°C, preferably at temperatures between 120 and 140°C.

e) In order to prepare a compound of general formula I wherein R_4 represents a 1H-tetrazolyl group:

Reaction of a compound of general formula



(VII),

wherein
R_1 to R_3 are defined as hereinbefore, with hydrazoic acid or the salts thereof.

The reaction is preferably carried out in a solvent such as benzene, toluene or dimethylformamide at temperatures

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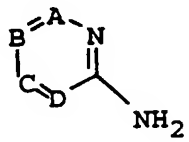
between 80 and 150°C, preferably at 125°C. Conveniently, either the hydrazoic acid is liberated during the reaction from an alkali metal azide, e.g. sodium azide, in the presence of a weak acid such as ammonium chloride or a tetrazolide salt obtained in the reaction mixture during the reaction with a salt of hydrazoic acid, preferably with aluminium azide or tributyl tin azide, which is also preferably produced in the reaction mixture by reacting aluminium chloride or tributyl tin chloride with an alkali metal azide such as sodium azide, is subsequently liberated by acidification with a dilute acid such as 2N hydrochloric or 2N sulphuric acid.

f) In order to prepare compounds of general formula I wherein R_2 represents one of the above-mentioned imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]pyridazin-2-yl or imidazo[2,1-b]-thiazol-6-yl groups:

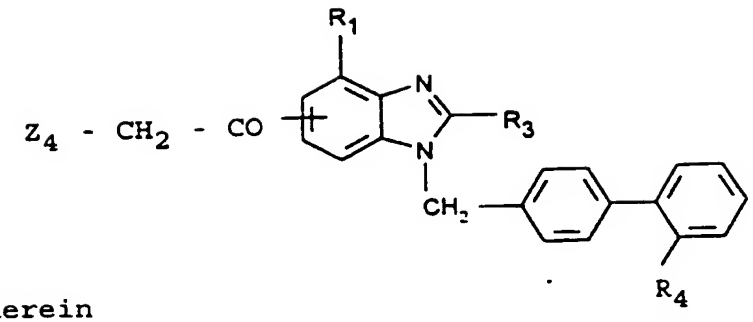
Reaction of a compound of general formula



(VIII),

wherein
one of the groups A, B, C or D represents an optionally methyl-substituted methine group or a nitrogen atom and the remaining groups A, B, C or D represent methine groups or A and B each represent a methine group and the -C=D- group represents a sulphur atom,
with a compound of general formula

B



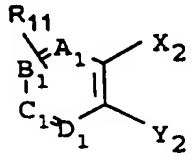
(IX),

wherein
R_1, R_3 and R_4 are defined as hereinbefore and
Z_4 represents a nucleophilic leaving group such as a halogen atom, e.g. a chlorine or bromine atom.

The reaction is expediently carried out in a solvent or mixture of solvents such as ethanol, isopropanol, benzene, glycol, glycolmonomethylether, dimethylformamide or dioxane, e.g. at temperatures between 0 and 150°C, preferably at temperatures between 20 and 100°C. However, the reaction may also be carried out without solvents.

g) In order to prepare compounds of general formula I wherein R_2 represents one of the above-mentioned benzimidazol-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl, imidazo[4,5-d]pyridazin-2-yl or purin-8-yl groups:

Cyclisation of a compound of general formula



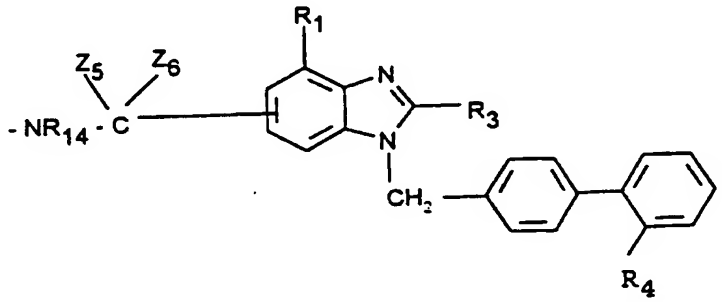
(X),

wherein
none, one or two of the groups A_1, B_1, C_1 or D_1 represent a nitrogen atom and

B

the remaining groups A_1, B_1, C_1 or D_1 represent methine groups,
R_{11} represents a hydrogen or fluorine atom or a methyl or trifluoromethyl group,

one of the groups X_2 or Y_2 represents an R_{13}-NH- group and the other X_2 or Y_2 group represents a group of general formula

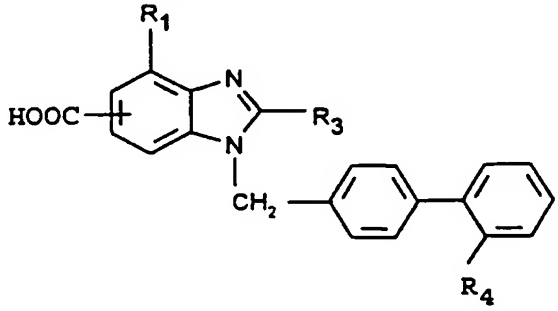


wherein R_1, R_3 and R_4 are defined as hereinbefore,
one of the groups R_{13} or R_{14} represents a hydrogen atom and the other R_{13} or R_{14} group represents a hydrogen atom, a C_{1-6}-alkyl group or a C_{3-7}-cycloalkyl group,
Z_5 and Z_6, which may be identical or different, represent optionally substituted amino groups or hydroxy or mercapto groups optionally substituted by lower alkyl groups or
Z_5 and Z_6 together represent an oxygen or sulphur atom, an optionally C_{1-3}-alkyl substituted imino group, or an alkylenedioxy or alkylenedithio group each having 2 or 3 carbon atoms, optionally followed by reduction of an N-oxide thus obtained and optional hydrolysis.

The cyclisation is conveniently carried out in a solvent or mixture of solvents such as ethanol, isopropanol, glacial acetic acid, benzene, chlorobenzene, toluene, xylene, glycol, glycolmonomethylether, diethyleneglycol-dimethylether, sulpholan, dimethylformamide, tetralin or in an excess of the acylating agent used to prepare the compound of general formula X, e.g. in the corresponding

nitrile, anhydride, acid halide, ester or amide, e.g. at temperatures between 0 and 250°C, but preferably at the boiling temperature of the reaction mixture, optionally in the presence of a condensing agent such as phosphorus oxychloride, thionylchloride, sulphurylchloride, sulphuric acid, p-toluenesulphonic acid, methanesulphonic acid, hydrochloric acid, phosphoric acid, polyphosphoric acid, acetic acid anhydride or optionally in the presence of a base such as potassium ethoxide or potassium tert.-butoxide. However, the cyclisation may also be carried out without a solvent and/or condensing agent.

However, it is particularly advantageous to perform the reaction by preparing a compound of general formula X in the reaction mixture by reducing a corresponding o-nitro-amino compound, optionally in the presence of a carboxylic acid of general formula



, (XI)

wherein

R_1, R_3 and R_4 are defined as hereinbefore, or by acylating a corresponding o-diamino compound with a carboxylic acid of general formula XI.

When the reduction of the nitro group is broken off at the hydroxylamine stage, subsequent cyclisation produces the N-oxide of a compound of general formula I. The N-oxide thus obtained is then converted by reduction into a corresponding compound of general formula I.

The subsequent reduction of an N-oxide thus obtained is

preferably carried out in a solvent such as water, water/ethanol, methanol, glacial acetic acid, ethyl acetate or dimethylformamide with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid such as acetic, hydrochloric or sulphuric acid, with salts such as iron(II)sulphate, tin(II)chloride or sodium dithionite, or with hydrazine in the presence of Raney nickel at temperatures between 0 and 50°C, but preferably at ambient temperature.

The subsequent hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trichloroacetic or trifluoroacetic acid in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxane at temperatures between -10°C and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture. When hydrolysis is carried out in the presence of an organic acid such as trichloroacetic or trifluoroacetic acid, any alcoholic hydroxy groups present may simultaneously be converted into a corresponding acyloxy group such as the trifluoroacetoxy group.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, amino or alkylamino groups may be protected during the reaction by conventional protecting groups which are split off again after the reaction.

Examples of protecting groups for a hydroxy group are trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.-butyl, benzyl and tetrahydropyranyl groups and

protecting groups for an amino, alkylamino or imino group include the acetyl, benzoyl, ethoxycarbonyl and benzyl groups.

The optional subsequent cleaving of a protecting group is preferably carried out by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as hydrochloric or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide at temperatures between 0 and 100°C, preferably at the boiling temperature of the reaction mixture. However, a benzyl group is preferably split off by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at ambient temperature, under a hydrogen pressure of 1 to 7 bar, preferably 3 to 5 bar.

An isomer mixture of a compound of general formula I thus obtained may if desired be resolved by chromatography using a substrate such as silica gel or aluminium oxide.

Moreover, the compounds of general formula I obtained may be converted into the acid addition salts thereof, more particularly for pharmaceutical use the physiologically acceptable salts thereof with inorganic or organic acids. Suitable acids for this purpose include hydrochloric, hydrobromic, sulphuric, phosphoric, fumaric, succinic, lactic, citric, tartaric or maleic acid.

Furthermore, the new compounds of general formula I thus

obtained, if they contain a carboxy or 1H-tetrazolyl group, may if desired subsequently be converted into the salts thereof with inorganic or organic bases, more particularly for pharmaceutical use into the physiologically acceptable addition salts thereof. Suitable bases include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II to XI used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature.

Thus, for example, a compound of general formula II is obtained by alkylation of a corresponding o-amino-nitro compound and subsequent reduction of the nitro group.

A compound of general formula III, V, VI, VII, IX or X used as starting material is obtained by acylation of a corresponding o-phenylenediamine or a corresponding o-amino-nitro compound, followed by reduction of the nitro group and subsequent cyclisation of an o-diamino-phenyl compound thus obtained, optionally followed by the cleaving of any protecting group used or by cyclisation of a correspondingly substituted benzimidazole with a corresponding amine or by NH-alkylation of a corresponding 1H-benzimidazole, whilst the isomer mixture thus obtained may subsequently be resolved by conventional methods, e.g. chromatography. Some of the starting compounds mentioned above are described in EP-A-0 392 317.

For example, 2-n-butyl-5-(imidazo[1,2-a]pyridin-2-yl)-3H-benzimidazole is obtained by reacting p-amino-acetophenone with butyric acid chloride, followed by nitration, bromination, cyclisation with 2-aminopyridine

to form the 6-n-butanoylamido-3-(imidazo[1,2-a]pyridin-2-yl)-nitrobenzene, which is subsequently converted into the desired compound by cyclisation, after reduction of the nitro group, or

2-n-butyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-1H-benzimidazole may be obtained by nitration of methyl 3-methyl-4-n-butanoylamido-benzoate, subsequent reduction of the nitro group and cyclisation to yield 2-n-butyl-4-methyl-6-methoxycarbonyl-1H-benzimidazole, which is then converted into the desired compound using 2-methylamino-aniline with cyclisation.

The new compounds of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties. They are angiotensin antagonists, particularly angiotensin-II-antagonists.

By way of example, the following compounds were tested for their biological effects as described hereinafter:

A = 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid,

B = 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

C = 4'-[[2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

D = 4'-[[2-n-butyl-6-(2,3-dimethylmaleic acid imino)-4-methyl-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid semihydrate,

E = 4'-[(2-cyclopropyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

F = 4'-[(2-n-propyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

G = 4'-[(2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyrimidin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

H = 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

I = 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

J = 4'-[(2-n-propyl-4-chloro-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl-hydrochloride and

K = 4'-[[2-n-propyl-4-methyl-6-(imidazo[2,1-b]thiazol-6-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

Description of method: Angiotensin II-receptor bonding

The tissue (rats lung) is homogenised in Tris-buffer (50 mMol Tris, 150 mMol NaCl, 5 mMol EDTA, pH 7.40) and centrifuged twice for 20 minutes at 20,000 x g. The finished pellets are resuspended in incubating buffer (50 mMol Tris, 5 mMol $MgCl_2$, 0.2% BSA, pH 7.40) 1:75, based on the moist weight of the tissue. Each 0.1 ml of homogenate is incubated for 60 minutes at 37°C with 50 pM [^{125}I]-antiotensin II (NEN, Dreieich, FRG) with

B

increasing concentrations of the test substance in a total volume of 0.25 ml. Incubation is ended by rapid filtration through glass fibre filter mats. The filters are each washed with 4 ml of ice cold buffer (25 mMol Tris, 2.5 mMol $MgCl_2$, 0.1% BSA, pH 7.40). The bound radioactivity is measured using a gamma-counter. The corresponding IC_{50} value is obtained from the dose-activity curve.

In the test described, substances A to K show the following IC_{50} values:

Substance	IC_{50} [nM]
A	3.7
B	14.0
C	1.2
D	20.0
E	12.0
F	26.0
G	3.4
H	1.2
I	1.7
J	20.0
K	7.8

In addition, compounds A, B, C, D, E and G were tested on conscious renally hypertensive rats for their effect after oral administration using methods known from the literature. At a dosage of 10 mg/kg these compounds exhibited a hypotensive effect.

Moreover, when the above-mentioned compounds were administered in a dose of 30 mg/kg i.v. no toxic side effects, e.g. negative inotropic effects or disorders in heart rhythm, were observed. The compounds are therefore well tolerated.

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In view of their pharmacological properties, the new compounds and the physiologically acceptable addition salts thereof are suitable for the treatment of hypertension and cardiac insufficiency and also for treating ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), for the prevention of the progression of cardiac insufficiency after myocardial infarction and for treating diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases.

The new compounds and the physiologically acceptable addition salts thereof are also suitable for treating pulmonary diseases, e.g. lung oedema and chronic bronchitis, for preventing arterial re-stenosis after angioplasty, for preventing thickening of blood vessel walls after vascular operations, and for preventing arteriosclerosis and diabetic angiopathy. In view of the effects of angiotensin on the release of acetylcholine and dopamine in the brain, the new angiotensin antagonists are also suitable for alleviating central nervous system disorders, e.g. depression, Alzheimer's disease, Parkinson syndrome, bulimia and disorders of cognitive function.

The dosage required to achieve these effects in adults is appropriately, when administered intravenously, 20 to 100 mg, preferably 30 to 70 mg, and, when administered orally, 50 to 200 mg, preferably 75 to 150 mg, 1 to 3 times a day. For this purpose, the compounds of general formula I prepared according to the invention, optionally in conjunction with other active substances, such as hypotensives, diuretics and/or calcium antagonists, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone,

citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene-glycol, propylene-glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

Additional active substances which may be included in the combinations mentioned above might be, for example, bendroflumethiazide, chlorothiazide, hydrochloro-thiazide, spironolactone, benzothiazide, cyclothiazide, ethacrinic acid, furosemide, metoprolol, prazosine, atenolol, propranolol, (di)hydralazine-hydrochloride, diltiazem, felodipin, nicardipin, nifedipin, nisoldipin and nitrendipin. The dosage for these active substances is appropriately one fifth of the lowest recommended dose up to 1/1 of the normally recommended dose, i.e., for example, 15 to 200 mg of hydrochlorothiazide, 125 to 2000 mg of chlorothiazide, 15 to 200 mg of ethacrinic acid, 5 to 80 mg of furosemide, 20 to 480 mg of propranolol, 5 to 60 mg of felodipine, 5 to 60 mg of nifedipin or 5 to 60 mg of nitrendipin.

The Examples which follow are intended to illustrate the invention:

Example A

4'-[[2-n-Butyl-7-[5-(imidazol-1-yl)-pentyloxy]-4-methyl-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid hydrate

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0.7 g (1.15 mMol) of tert.-butyl 4'-[[2-n-butyl-7-[5-(imidazol-1-yl)-pentyloxy]-4-methyl-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate are dissolved in 35 ml of methylene chloride, 5 ml of trifluoroacetic acid are added and the mixture is stirred for 12 hours at ambient temperature. It is diluted with methylene chloride and extracted with water and with saturated sodium bicarbonate solution. The organic phase is dried over sodium sulphate and evaporated down in vacuo. The crude product thus obtained is purified over a silica gel column (particle size: 0.063-0.02 mm, ethyl acetate/ethanol/ammonia - 90:10:0.1) and crystallised from acetone.
Yield: 0.19 g (29.9% of theory),
Melting point: 185-187°C
$C_{34}H_{38}N_4O_3 \times H_2O$ (550.70)

Calculated:	C 71.81	H 7.09	N 9.85
Found:	72.03	7.19	9.71

Mass spectrum: m/e = M^+ 550

Example 1

4'-[[2-n-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.-butyl 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in dimethylformamide.
Yield: 63.9% of theory,
Melting point: 261-263°C
$C_{33}H_{30}N_4O_2$ (514.60)

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Calculated:	C 77.02	H 5.87	N 10.89
Found:	76.90	5.85	10.99

The following compounds are obtained analogously to Example 1:

4'-[[2-n-propyl-4-methyl-6-(1-n-propylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

4'-[[2-n-propyl-4-methyl-6-(1-n-hexylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

4'-[[2-n-propyl-4-methyl-6-(1-cyclopropylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

4'-[[2-n-propyl-4-methyl-6-(1-cyclohexylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

Example 2

4'-[[2-n-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

4.3 g (66 mMol) of sodium azide and 3.5 g (66 mMol) of ammonium chloride are added to a solution of 1.60 g (3.3 mMol) of 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl in 50 ml of dimethylformamide and the mixture is stirred for 24 hours at 140°C. Then water is added and the precipitate is removed by suction filtering. The crude product thus obtained is purified by chromatography over silica gel (300 g of silica gel, methylene chloride + 6% ethanol).
Yield: 900 mg (51% of theory),
Melting point: 228-230°C

$C_{33}H_{30}N_8$ (538.70)
Calculated: C 73.58 H 5.61 N 20.80
Found: 73.48 5.55 20.70

The following compounds are obtained analogously to Example 2:

4'-[[2-n-propyl-4-methyl-6-(1-n-hexylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-4-methyl-6-(1-cyclobutylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-4-methyl-6-(1-cyclohexylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Example 3

4'-[[2-n-Propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 49.0% of theory,
Melting point: Sintering from 186°C
$C_{29}H_{31}N_7O_2S$ (541.70)
Calculated: C 64.30 H 5.77 N 18.10 S 5.92
Found: 64.10 5.39 18.01 5.98

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Example 4

4'-[[2-Ethyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 2 from 4'-[[2-ethyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 60.0% of theory,
Melting point: amorphous, sintering from 194°C
$C_{28}H_{29}N_7O_2S$ (527.70)

Calculated:	C	63.74	H	5.54	N	18.58	S 6.08
Found:		63.83		5.66		18.41	5.82

Example 5

4'-[[2-n-Butyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 2 from 4'-[[2-n-butyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 48.0% of theory,
Melting point: amorphous, sintering from 183°C
$C_{30}H_{33}N_7O_2S$ (555.70)

Calculated:	C	64.84	H	5.99	N	17.64	S 5.77
Found:		64.53		5.66		17.63	5.55

Example 6

4'-[[2-n-Propyl-4-ethyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 2 from 4'-[[2-n-propyl-4-ethyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 27.0% of theory,

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Melting point: amorphous, sintering from 189°C

$C_{30}H_{33}N_7O_2S$ (555.70)

Calculated:	C	64.84	H	5.99	N	17.64	S 5.77
Found:		64.81		5.68		17.87	5.31

Example 7

4'-[[2-Ethyl-4-ethyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-ethyl-4-ethyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.

Yield: 39.0% of theory,

Melting point: amorphous, sintering from 212°C

$C_{29}H_{31}N_7O_2S$ (541.70)

Calculated:	C	64.30	H	5.77	N	18.10	S 5.92
Found:		64.30		5.51		17.99	5.59

Example 8

4'-[[2-n-Propyl-4-isopropyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-propyl-4-isopropyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.

Yield: 22.0% of theory,

Melting point: amorphous

$C_{31}H_{35}N_7O_2S$ (569.70)

Calculated:	C	65.35	H	6.19	N	17.21	S 5.63
Found:		65.13		6.10		17.54	5.40

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Example 9

4'-[[2-Ethyl-4-isopropyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-ethyl-4-isopropyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethyl-formamide.
Yield: 24.0% of theory,
Melting point: amorphous, sintering from 209°C
$C_{30}H_{33}N_7O_2S$ (555.70)

Calculated:	C	64.84	H	5.99	N	17.64	S 5.77
Found:		64.99		5.71		17.43	5.71

Example 10

4'-[[2-n-Propyl-4-trifluoromethyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-propyl-4-trifluoromethyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethyl-formamide.
Yield: 17.0% of theory,
Melting point: 199-203°C
$C_{29}H_{28}F_3N_7O_2S$ (595.70)

Calculated:	C	58.48	H	4.74	N	16.46	
Found:		58.28		4.43		16.22	

Example 11

4'-[[2-n-Butyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.-butyl 4'-[[2-n-butyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and

B

trifluoroacetic acid in methylene chloride.
Yield: 48.0% of theory,
Melting point: 233-235°C
$C_{34}H_{32}N_4O_2$ (528.70)
Calculated: C 77.25 H 6.10 N 10.60
Found: 77.10 5.98 10.46

Example 12

4'-[[2-n-Butyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-butyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 41.0% of theory,
Melting point: 235-237°C
$C_{34}H_{32}N_8$ (552.70)
Calculated: C 73.89 H 5.84 N 20.28
Found: 73.67 5.81 19.93

The following compounds are obtained analogously to Example 12:

4'-[[2-n-butyl-4-methyl-6-(1-ethylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-butyl-4-methyl-6-(1-cyclopropylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-butyl-4-methyl-6-(1-n-pentylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-butyl-4-methyl-6-(1-cyclopentylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

B

Example 13

4'-[[2-n-Propyl-4-methyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-propyl-4-methyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethyl-formamide.
Yield: 51.0% of theory,
Melting point: amorphous, from 140°C (sintering)
$C_{30}H_{31}N_7O$ (505.60)
Calculated: C 71.26 H 6.18 N 19.39
Found: 71.08 6.22 19.47

Example 14

4'-[[2-n-Butyl-4-methyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-butyl-4-methyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethyl-formamide.
Yield: 39.0% of theory,
Melting point: amorphous, from 128°C (sintering)
$C_{31}H_{33}N_7O$ (519.70)
Calculated: C 71.65 H 6.40 N 18.87
Found: 71.44 6.23 18.59

Example 15

4'-[[2-n-Propyl-4-methyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared from 4'-[[2-n-propyl-4-methyl-6-(2-oxo-piperidin-1-yl)-benzimidazol-1-yl]-methyl]-2-(2-triphenylmethyl-tetrazol-5-yl)biphenyl by cleaving the

B

triphenylmethyl group with methanolic hydrochloric acid.
Yield: 51.0% of theory,
Melting point: amorphous, sintering from 115°C
$C_{30}H_{31}N_7O$ (505.60)

Calculated:	C 71.26	H 6.18	N 19.39
Found:	71.51	6.39	19.09

Example 16

4'-[[2-n-Propyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.-butyl 4'-[[2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 38.0% of theory,
Melting point: 195-197°C (after evaporation and without recrystallisation)
Melting point: 299-303°C (methylene chloride/ethanol = 20:1)
$C_{32}H_{28}N_4O_2$ (500.60)

Calculated:	C 76.78	H 5.64	N 11.19
Found:	76.55	5.61	10.87

Example 17

4'-[[2-n-Propyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 21.0% of theory,
Melting point: sintering from 181°C
$C_{32}H_{28}N_8$ (524.60)

Calculated:	C 73.26	H 5.38	N 21.36

B

Found: 73.10 5.24 21.13

The following compound may be prepared analogously to Example 17:

4'-[[2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyrimidin-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Example 18

4'-[[2-n-Butyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.-butyl 4'-[[2-n-butyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 51.0% of theory,
Melting point: 194-197°C
$C_{33}H_{30}N_4O_2$ (514.60)
Calculated: C 77.02 H 5.88 N 10.89
Found: 76.81 5.78 10.64

Example 19

4'-[[2-n-Butyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-butyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 26.0% of theory,
$C_{33}H_{30}N_8$ (538.60)
Calculated: C 73.58 H 5.61 N 20.80
Found: 73.39 5.40 20.92

Example 20

4'-[[2-n-Propyl-4-methyl-6-(imidazo[1,2-a]pyrimidin-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.-butyl 4'-[[2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyrimidin-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 47% of theory,
Melting point: 224-226°C (after evaporation and without recrystallisation)
Melting point: 294-297°C (methylene chloride/ethanol = 20:1)
$C_{31}H_{27}N_5O_2$ (501.60)

Calculated:	C 74.23	H 5.43	N 13.96
Found:	74.10	5.31	13.66

Example 21

4'-[[2-n-Propyl-4-methyl-6-(imidazo[2,1-b]thiazol-6-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.-butyl 4'-[[2-n-propyl-4-methyl-6-(imidazo[2,1-b]thiazol-6-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 43% of theory,
Melting point: 192-195°C (after evaporation and without recrystallisation)
Melting point: >300°C (methylene chloride/ethanol - 20:1)
$C_{30}H_{26}N_4O_2S$ (506.64)

Calculated:	C 71.12	H 5.17	N 11.06	S 6.33
Found:	70.97	5.19	10.88	6.09

B

Example 22

4'-[[2-n-Propyl-4-methyl-6-(imidazo[2,1-b]thiazol-6-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-propyl-4-methyl-6-(imidazo[2,1-b]thiazol-6-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 21% of theory,
Melting point: amorphous, sintering from 196°C
$C_{30}H_{26}N_8S$ (530.67)

Calculated:	C	67.90	H	4.94	N	21.12	S 6.04
Found:		67.77		4.84		21.00	5.87

Example 23

4'-[[2-n-Propyl-4-methyl-6-(benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[[2-n-propyl-4-methyl-6-(benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 28% of theory,
Melting point: 202-205°C
$C_{32}H_{28}N_8$ (524.64)

Calculated:	C	73.26	H	5.38	N	21.36
Found:		73.01		5.22		21.56

The following compounds are obtained analogously to Example 23:

4'-[[2-ethyl-4-methyl-6-(benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-butyl-4-methyl-6-(benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

B

4'-[[2-n-propyl-4-methyl-6-(1-n-hexyl-benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-4-methyl-6-(1-cyclopropyl-benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[[2-n-propyl-4-methyl-6-(1-cyclohexyl-benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Example 24

4'-[[2-n-Propyl-4-methyl-6-(benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.-butyl 4'-[[2-n-propyl-4-methyl-6-(benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 43% of theory,
Melting point: 239-242°C
$C_{32}H_{28}N_4O_2$ (500.61)

Calculated:	C 76.78	H 5.64	N 11.19
Found:	76.55	5.60	11.41

The following compounds are obtained analogously to Example 24:

4'-[[2-ethyl-4-methyl-6-(benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

4'-[[2-n-butyl-4-methyl-6-(benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

4'-[[2-n-propyl-4-methyl-6-(1-n-hexyl-benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic

B

acid

4'-[[2-n-propyl-4-methyl-6-(1-cyclopropyl-benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

4'-[[2-n-propyl-4-methyl-6-(1-cyclohexyl-benzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

Example 25

4'-[[2-n-Butyl-6-(2,3-dimethylmaleic acid imino)-4-methyl-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid-semihydrate

---

Prepared analogously to Example A from tert.butyl 4'-[[2-n-butyl-6-(2,3-dimethylmaleic acid imino)-4-methyl-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 88.9% of theory,
Melting point: 321-322°C
$C_{32}H_{31}N_3O_4 \times 0.5\ H_2O$ (530.62)

Calculated:	C 72.43	H 6.08	N 7.92
Found:	72.89	6.16	7.89

Example 26

4'-[[6-(2,3-Dimethylmaleic acid imino)-2-n-propyl-4-methyl-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid semihydrate

---

Prepared analogously to Example A from tert.butyl 4'-[[6-(2,3-dimethylmaleic acid imino)-2-n-propyl-4-methyl-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 75.4% of theory,
Melting point: 329-331°C
$C_{31}H_{29}N_3O_4 \times 0.5\ H_2O$ (516.60)

B

Calculated:	C 72.08	H 5.85	N 8.13
Found:	72.04	5.84	7.96

Example 27

4'-[(2-n-Propyl-4-ethyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.butyl 4'-[(2-n-propyl-4-ethyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 64% of theory,
Melting point: 217-219°C
$C_{34}H_{32}N_4O_2$ (528.70)

Calculated:	C 77.24	H 6.10	N 10.60
Found:	77.12	6.09	10.75

Example 28

4'-[(2-n-Propyl-4-ethyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-ethyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 15% of theory,
Melting point: 215-217°C
$C_{34}H_{32}N_8$ (552.70)

Calculated:	C 73.89	H 5.84	N 20.28
Found:	73.66	6.02	20.56

Example 29

4'-[(2-Cyclopropyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.butyl 4'-

B

[(2-cyclopropyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 52% of theory,
Melting point: 244-246°C
$C_{33}H_{28}N_4O_2$ (512.60)

Calculated:	C	77.32	H	5.51	N 10.93
Found:		77.75		5.71	10.94

Example 30

4'-[(2-Cyclopropyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[(2-cyclopropyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 59% of theory,
Melting point: 245-247°C
$C_{33}H_{28}N_8$ (536.65)

Calculated:	C	73.86	H	5.26	N 20.88
Found:		73.95		5.42	20.90

Example 31

4'-[(2-Cyclobutyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.butyl 4'-[(2-cyclobutyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 63% of theory,
Melting point: 189-191°C
$C_{34}H_{30}N_4O_2$ (526.60)

Calculated:	C	77.55	H	5.74	N 10.64

B

Found: 77.35 5.92 10.40

Example 32

4'-[(2-Cyclobutyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[(2-cyclobutyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 61% of theory,
Melting point: 197-199°C
$C_{34}H_{30}N_8$ (550.70)
Calculated: C 74.16 H 5.49 N 20.35
Found: 74.12 5.74 20.67

Example 33

4'-[(2-n-Propyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.butyl 4'-[(2-n-propyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-y)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 34% of theory,
Melting point: 250-252°C
$C_{33}H_{29}FN_4O_2$ (532.60)
Calculated: C 74.42 H 5.49 N 10.52
Found: 74.14 5.64 10.54

The following compound is obtained analogously to Example 33:

4'-[(2-n-propyl-4-methyl-6-(pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

B

Example 34

4'-[(2-n-Propyl-4-methyl-6-(imidazo[1,2-a]pyrimidin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyrimidin-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 16.5% of theory,
Melting point: from 275°C (decomp.)
$C_{31}H_{27}N_9 \times H_2O$ (543.65)

Calculated:	C 68.49	H 5.38	N 23.19
Found:	68.25	5.50	23.37

The following compound is obtained analogously to Example 34:

4'-[(2-n-propyl-4-methyl-6-(pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Example 35

4'-[(2-n-Propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.butyl 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo-[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 67% of theory,
Melting point: from 240°C (sinters)
$C_{32}H_{32}N_4O_2$ (504.64)

Calculated:	C 76.16	H 6.39	N 11.10
Found:	75.94	6.46	11.20

B

The following compounds are obtained analogously to Example 35:

4'-[(2-n-butyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

4'-[(2-ethyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

Example 36

4'-[(2-n-Propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo-[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 73.5% of theory,
Melting point: from 275°C (decomp.)
$C_{32}H_{32}N_8$ (528.67)

Calculated:	C 72.70	H 6.10	N 21.20
Found:	72.40	6.07	21.48

The following compounds are obtained analogously to Example 36:

4'-[(2-n-butyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo-[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[(2-ethyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo-[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

B

Example 37

4'-[(2-n-Propyl-4-methyl-6-(1-methyl-6-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.butyl 4'-[(2-n-propyl-4-methyl-6-(1-methyl-6-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 76% of theory,
Melting point: 243-245°C
$C_{33}H_{29}FN_4O_2$ (532.60)

Calculated:	74.42	H 5.49	N 10.52
Found:	74.74	5.52	10.77

Mass spectrum: m/e = 532

Example 38

4'-[(2-n-Propyl-4-chloro-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example A from tert.butyl 4'-[(2-n-propyl-4-chloro-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 52.7% of theory,
Melting point: 292-295°C
$C_{32}H_{27}CN_4O_2$ (535.06)
R_f value: 0.30 (silica gel; methylene chloride/ethanol = 19:1)

Calculated:	C 71.90	H 5.08	N 10.45	Cl 6.63
Found:	71.29	5.21	10.40	6.76

B

Example 39

4'-[(2-n-Propyl-4-chloro-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl hydrochloride

---

Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-chloro-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 54.8% of theory,
Melting point: sintering from 204°C
$C_{32}H_{27}ClN_8 \times HCl$ (595.55)
R_f value: 0.20 (silica gel; petroleum ether/ethyl acetate = 1:1 and 1% glacial acetic acid)

Calculated:	C 62.55	H 4.71	N 18.85	Cl 11.85
Found:	62.34	4.97	18.84	11.57

Example 40

4'-[(2-n-Propyl-4-methyl-6-(1-methyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

a) 3-Methyl-4-butyrylamino-5-nitro-acetophenone

32.6 g (148 mmol) of 3-methyl-4-butyrylamino-acetophenone are added in batches at -15°C to 300 ml of fuming nitric acid with stirring, and stirred for a further 30 minutes at -15°C. The reaction mixture is then poured onto 3 litres of ice, with stirring, the crude product precipitated is suction filtered, washed with 400 ml of water, dried and purified by recrystallisation from ethanol/diethylether (1:1).
Yield: 23.8 g (61.0% of theory),
R_f value: 0.32 (silica gel; methylene chloride),
R_f value: 0.48 (silica gel; methylene chloride/methanol = 50:1).

b) 3-Methyl-4-butyrylamino-5-nitro-1-bromoacetophenone

A solution of 16.0 g (200 mmol) of bromine in 140 ml of dioxane is added dropwise to a solution of 23.8 g (90 mmol) of 3-methyl-4-butyrylamino-5-nitro-acetophenone in 900 ml of dichloromethane at ambient temperature, with stirring, so slowly that total decolorisation of the reaction mixture occurs constantly. The mixture is then stirred for a further two hours, then the reaction mixture is evaporated to dryness in vacuo, the residue obtained is triturated with about 20 ml of dichloromethane/diethylether (1:1), suction filtered and then dried. 23g (74% of theory) of 3-methyl-4-butyrylamino-5-nitro-ω-bromoacetophenone are thus obtained, still containing about 10% starting material. The product is further reacted without any more purification.

R_f value: 0.69 (silica gel; methylene chloride/methanol = 50:1)

R_f value: 0.84 (silica gel; methylene chloride/methanol = 9:1).

c) 2-Butyrylamino-3-nitro-5-(imidazo-4-yl)-toluene

A solution of 6.8 g (20 mmol) of 3-methyl-4-butyrylamino-5-nitro-ω-bromoacetophenone in 20 ml of formamide is heated to 140°C for two hours. The cooled solution is then poured into about 50 ml of 1N ammonia and stirred for about 15 minutes. The crude product precipitated is suction filtered, washed with about 50 ml of water and dried. In this way, 4.4 g (75% of theory) of the product are obtained, which is further reacted without any more purification.

R_f value: 0.29 (silica gel; methylene chloride/methanol = 9:1)

d) 2-Butyrylamino-3-nitro-5-(1-methyl-imidazol-4-yl)-toluene

1.3 g (9.5 mmol) of methyliodide are added dropwise at

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ambient temperature to a solution of 2.5 g (8.7 mmol) of 2-butyrylamino-3-nitro-5-(imidazol-4-yl)-toluene and 5.2 g (30 mmol) of potassium carbonate dihydrate in 30 ml of dimethylsulfoxide and the mixture is then stirred for two hours. The reaction mixture is then stirred into about 150 ml of water and extracted four times with 25 ml of ethylacetate. The organic extracts are washed with about 30 ml of water, dried and evaporated down. The crude product thus obtained is purified by column chromatography (300 g of silica gel, eluant: methylene chloride/methanol = 30:1).
Yield: 640 mg (24% of theory),
R_f value: 0.54 (silica gel; methylene chloride/methanol = 9:1)

e) 2-Butyrylamino-3-amino-5-(1-methyl-imidazol-4-yl)-toluene

640 mg (2.1 mmol) of 2-butyrylamino-3-nitro-5-(1-methyl-imidazol-4-yl)-toluene are hydrogenated in 30 ml of methanol after the addition of about 200 mg of palladium/charcoal (20%) at ambient temperature under a hydrogen pressure of 5 bar. After all the hydrogen has been absorbed the catalyst is removed by filtering and the filtrate is evaporated down. The crude product obtained is further reacted without any more purification.
Yield: 600 mg (100% of theory),
R_f value: 0.23 (silica gel; methylene chloride/methanol = 9:1)

f) 2-n-Propyl-4-methyl-6-(1-methyl-imidazol-4-yl)-benzimidazole

600 mg (2.1 mmol) of 2-butyrylamino-3-amino-5-(1-methyl-imidazol-4-yl)-toluene are refluxed for one hour in 10 ml of glacial acetic acid. Then the mixture is evaporated to dryness in vacuo, the residue is mixed with about 15 ml of water, made alkaline with ammonia

and extracted four times with about 10 ml of ethylacetate. The organic extracts are washed with about 15 ml of water, dried and finally evaporated down. The crude product thus obtained is further reacted without any more purification.
Yield: 420 mg (79% of theory),
R_f value: 0.37 (silica gel; methylene chloride/methanol = 9:1)

g) Tert.butyl-4'-[(2-n-propyl-4-methyl-6-(1-methyl-imidazol-4-yl)-benzimidazol-1-yl)methyl]-biphenyl-2-carboxylate
280 mg (0.8 mmol) of tert.butyl-4'-bromomethyl-biphenyl-2-carboxylate are added to a solution of 200 mg (0.79 mmol) of 2-n-propyl-4-methyl-6-(1-methyl-imidazol-4-yl)-benzimidazole and 90 mg (0.8 mmol) of potassium tert.butoxide in 5 ml of dimethylsulfoxide and the mixture is stirred for 90 minutes at ambient temperature, then stirred into about 40 ml of water, extracted four times with about 10 ml of ethylacetate, then the organic extracts are washed with 10 ml of water, dried and evaporated to dryness. The crude product thus obtained is purified by column chromatography (100 g silica gel, eluant: dichloromethane/methanol = 30:1).
Yield: 230 mg (56% of theory),
R_f value: 0.61 (silica gel; methylene chloride/methanol = 9:1)

h) 4'-[2-n-Propyl-4-methyl-6-(1-methyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid
A solution of 230 mg (0.44 mmol) of tert.butyl-4'-[(2-n-propyl-4-methyl-6-(1-methyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and 2 ml of trifluoroacetic acid in 10 ml of dichloromethane was stirred overnight at ambient temperature and then evaporated to dryness. The residue was dissolved in

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about 5 ml of dilute sodium hydroxide solution, the solution was neutralised with acetic acid, the precipitate was suction filtered, washed with water and dried.
Yield: 120 mg (59% of theory);
Melting point: 293-295°C
R_f value: 0.39 (silica gel; methylene chloride/methanol = 9:1)

The following compounds are obtained analogously to Example 40:

4'-[(2-n-propyl-4-methyl-6-(1-ethyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

4'-[(2-n-propyl-4-methyl-6-(1-benzyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

4'-[(2-n-propyl-4-methyl-6-(1-isopropyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

Example 41

4'-[(2-n-Propyl-4-methyl-6-(1-methyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

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Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-methyl-6-(1-methyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 24% of theory,
Melting point: 255-257°C
R_f value: 0.24 (silica gel, methylene chloride/methanol = 9:1)
$C_{29}H_{28}N_8 \times H_2O$ (506.62)
Calculated: C 68.75 H 5.97 N 22.12
Found: 68.90 5.97 22.03

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The following compounds are obtained analogously to Example 41:

4'-[(2-n-propyl-4-methyl-6-(1-ethyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

4'-[(2-n-propyl-4-methyl-6-(1-benzyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

4'-[(2-n-propyl-4-methyl-6-(1-isopropyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Example 42

4'-[2-Ethyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 2 from 4'-[(2-ethyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 21% of theory,
Melting point: amorphous
R_f value: 0.27(silica gel, methylene chloride/ethanol = 9:1)
$C_{31}H_{30}N_8$ (514.64)

Calculated:	C 72.35	H 5.88	N 21.78
Found:	72.01	5.82	21.44

Example 43

4'-[(2-n-Propyl-4-methyl-6-(8-methyl-imidazo-[1,2-a]-pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

Prepared analogously to Example A from tert.butyl 4'-[(2-n-propyl-4-methyl-6-(8-methyl-imidazo-[1,2-a]-

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pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 87% of theory,
Melting point: 295-297°C
R_f value: 0.34 (silica gel, methylene chloride/ethanol = 9:1)
$C_{33}H_{30}N_4O_2 \times H_2O$ (532.65)

Calculated:	C 74.41	H 6.06	N 10.52
Found:	74.81	6.05	10.43

Example 44

4'-[(2-n-Propyl-4-methyl-6-(2-pyridyl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-methyl-6-(2-pyridyl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 56% of theory,
Melting point: from 136°C (decomp.)
$C_{30}H_{27}N_7 \times 0.5\ H_2O$ (494.60)

Calculated:	C 72.85	H 5.71	N 19.83
Found:	72.45	6.01	19.83

Example 45

4'-[(2-n-Propyl-4-methyl-6-(8-methyl-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-methyl-6-(8-methyl-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 19% of theory,
Melting point: amorphous
R_f value: 0.36 (silica gel, methylene chloride/ethanol = 9:1)

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$C_{33}H_{30}N_8$ (538.61)
Mass spectrum: m/e = 538

Example 46

4'-[(2-Ethyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

Prepared analogously to Example A from tert.butyl 4'-[2-ethyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 50% of theory,
Melting point: > 300°C
R_f value: 0.16 (silica gel, methylene chloride/ethanol = 9:1)

Example 47

4'-[(2-n-Propyl-4-methyl-6-(1-isopropyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

Prepared analogously to Example A from tert.butyl 4'-[(2-n-propyl-4-methyl-6-(1-isopropyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 84% of theory,
Melting point: 285-286°C
R_f value: 0.55 (silica gel, methylene chloride/methanol = 9:1)

Example 48

4'-[(2-n-Propyl-4-methyl-6-(1-isopropyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-methyl-6-(1-isopropyl-imidazol-4-yl)-benzimidazol-1-

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yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.
Yield: 18% of theory,
Melting point: amorphous
R_f value: 0.29 (silica gel, methylene chloride/methanol = 9:1)
$C_{31}H_{32}N_8$ (516.66)
Mass spectrum: m/e = 516

Example 49

4'-[(2-n-Propyl-4-methyl-6-(1-benzyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

Prepared analogously to Example A from tert.butyl 4'-[(2-n-propyl-4-methyl-6-(1-benzyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-biphenyl and trifluoroacetic acid in methylene chloride.

Example 50

4'-[(2-n-Propyl-4-methyl-6-(1-benzyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 2 from 4'-[(2-n-propyl-4-methyl-6-(1-benzyl-imidazol-4-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl and sodium azide in dimethylformamide.

Example 51

Ampoules containing 50 mg of active substance per 5 ml

Active substance	50 mg
KH_2PO_4	2 mg
$Na_2HPO_4 \times 2H_2O$	50 mg
NaCl	12 mg
Water for injections ad	5 ml

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Preparation:

The buffer substances and isotonic substance are dissolved in some of the water. The active substance is added and, once it has been completely dissolved, water is added to make up the required volume.

Example 52

Ampoules containing 100 mg of active substance per 5 ml

Active substance	100 mg
Methyl glucamine	35 mg
Glycofurol	1000 mg
Polyethyleneglycol-polypropylene-glycol block polymer	250 mg
Water for injections ad	5 ml

Preparation:

Methyl glucamine is dissolved in some of the water and the active substance is dissolved with stirring and heating. After the addition of solvents, water is added to make up the desired volume.

Example 53

Tablets containing 50 mg of active substance

Active substance	50.0 mg
Calcium phosphate	70.0 mg
Lactose	40.0 mg
Corn starch	35.0 mg
Polyvinylpyrrolidone	3.5 mg
Magnesium stearate	1.5 mg
	200.0 mg

B

Preparation:

The active substance, $CaHPO_4$, lactose and corn starch are uniformly moistened with an aqueous PVP solution. The mass is passed through a 2 mm screen, dried at 50°C in a circulating air dryer and screened again.

After the lubricant has been added, the granules are compressed in a tablet making machine.

Example 54

Coated tablets containing 50 mg of active substance

Active substance	50.0 mg
Lysine	25.0 mg
Lactose	60.0 mg
Corn starch	34.0 g
Gelatin	10.0 mg
Magnesium stearate	1.0 mg
	180.0 mg

Preparation:

The active substance is mixed with the excipients and moistened with an aqueous gelatin solution. After screening and drying the granules are mixed with magnesium stearate and compressed to form tablet cores.

The cores thus produced are covered with a coating by known methods. A colouring may be added to the coating suspension or solution.

Example 55

Coated tablets containing 100 mg of active substance

Active substance	100.0 mg
Lysine	50.0 mg
Lactose	86.0 mg
Corn starch	50.0 mg
Polyvinylpyrrolidone	2.8 mg
Microcrystalline cellulose	60.0 mg
Magnesium stearate	1.2 mg
	350.0 mg

Preparation:

The active substance is mixed with the excipients and moistened with an aqueous PVP solution. The moist mass is passed through a 1.5 mm screen and dried at 45°C. After drying, it is screened again and the magnesium stearate is added. This mixture is compressed into cores.

The cores thus produced are covered with a coating by known methods. Colourings may be added to the coating suspension or solution.

Example 56

Capsules containing 250 mg of active substance

Active substance	250.0 mg
Corn starch	68.5 mg
Magnesium stearate	1.5 mg
	320.0 mg

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Preparation:

The active substance and corn starch are mixed together and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The final mixture is packed into size 1 hard gelatine capsules.

Example 57

Oral suspension containing 50 mg of active substance per 5 ml

Active substance	50.0 mg
Hydroxyethylcellulose	50.0 mg
Sorbic acid	5.0 mg
70% sorbitol	600.0 mg
Glycerol	200.0 mg
Flavouring	15.0 mg
Water ad	5.0 ml

Preparation:

Distilled water is heated to 70°C. Hydroxyethyl-cellulose is dissolved therein with stirring. With the addition of sorbitol solution and glycerol the mixture is cooled to ambient temperature. At ambient temperature, sorbic acid, flavouring and active substance are added. The suspension is evacuated with stirring to remove any air. One dose of 50 mg is contained in 5.0 ml.

Example 58

Suppositories containing 100 mg of active substance

Active substance	100.0 mg
Solid fat	1600.0 mg
	1700.0 mg

Preparation:

The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed in the melt. It is cooled to 38°C and poured into slightly chilled suppository moulds.

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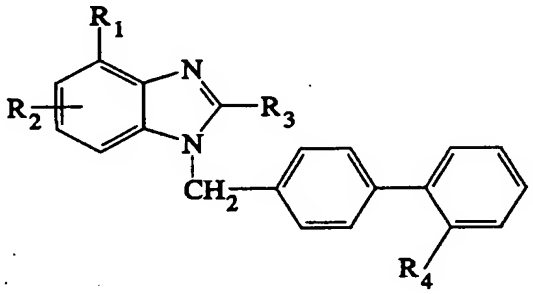
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Benzimidazoles of general formula



(I),

wherein

R^1 represents a fluorine, chlorine or bromine atom, an alkyl, cycloalkyl, fluoromethyl, difluoromethyl or trifluoromethyl group and

R^2 represents a 5-, 6- or 7-membered alkyleneimino or alkenyleneimino group, optionally substituted by one or two alkyl groups or by a tetramethylene or pentamethylene group, wherein a methylene group may be replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by an alkyl or phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by C_{1-6}-alkyl or a cycloalkyl group, whilst the phenyl nucleus of the benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl

group may additionally be substituted by a fluorine atom or by a methyl or trifluoromethyl group, R_2 may represent an imidazo [2,1-b] thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]-pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]-pyridin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]-pyrazin-2-yl, imidazo[1,2-b]-pyridazin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group,

a pyridyl group or

a carbon attached imidazolyl group optionally substituted in the 1-position by an alkyl or benzyl group, and which may also be substituted in the carbon skeleton by an alkyl group,

R_3 represents a C_{1-5}-alkyl group or a C_{3-5}-cycloalkyl group and

R_4 represents a carboxy or 1H-tetrazolyl group,

and the salts thereof with inorganic or organic acids or bases,

whilst, unless otherwise specified, an alkyl moiety as mentioned hereinbefore may in each case contain 1 to 3 carbon atoms and a cycloalkyl moiety mentioned hereinbefore may contain from 3 to 7 carbon atoms.

2. Benzimidazoles of general formula I according to claim 1, wherein

R_1 represents a chlorine atom, or a C_{1-3}-alkyl or a trifluoromethyl group,

R_2 represents a 5-, 6- or 7-membered alkyleneimino group wherein a methylene group is replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by a C_{1-3}-alkyl or phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by a C_{1-6}-alkyl or by a cycloalkyl group, whilst the phenyl nucleus of the benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group may additionally be substituted by a fluorine atom or by a methyl or trifluoromethyl group, or R_2 may represent an imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]-pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]-pyridin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]-pyrazin-2-yl, imidazo[1,2-b]-pyridazin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group,

a pyridyl group or

an imidazol-4-yl group substituted in the 1-position by a C_{1-3} alkyl group or by a benzyl group which may also be substituted in the carbon skeleton by a C_{1-3} alkyl group,

R_3 represents a C_{1-5}-alkyl group or a C_{3-5}-cycloalkyl group and

R_4 represents a carboxy or 1H-tetrazolyl group,

and the salts thereof with inorganic or organic acids or bases.

3. Benzimidazoles of general formula I according to claim 1, wherein

R_1 represents a methyl group or a chlorine atom and

R_2 represents a 5-, 6- or 7-membered alkyleneimino group, wherein a methylene group is replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by a C_{1-3}-alkyl or phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by a C_{1-3}-alkyl group, whilst the phenyl nucleus of the benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group may additionally be substituted by a fluorine atom, or R_2 may represent an imidazo[1,2-a]-pyridin-2-yl group, 5,6,7,8-tetrahydro-imidazo[1,2-a]-pyridin-2-yl, imidazo[1,2-a]-pyrimidin-2-yl or imidazo[2,1-b]thiazol-6-yl group,

an imidazol-4-yl group substituted in the 1-position by a C_{1-3} alkyl group,

R_3 represents a C_{1-5}-alkyl group or a C_{3-5}-cycloalkyl group and

R_4 represents a carboxy or 1H-tetrazolyl group,

and the salts thereof with inorganic or organic acids or bases.

4. The following benzimidazoles of general formula I according to claim 1:

(a) 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid,

(b) 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

(c) 4'-[[2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

(d) 4'-[[2-n-butyl-6-(2,3-dimethylmaleic acid imino)-4-methylbenzimidazol-1-yl]methyl]-biphenyl-2-carboxylic acid,

(e) 4'-[2-cyclopropyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

(f) 4'-[(2-n-propyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

(g) 4'-[(2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyrimidin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

(h) 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

(i) 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

(j) 4'-[(2-n-propyl-4-chloro-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

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(k) 4'-[[2-n-propyl-4-methyl-6-(imidazo[2,1-b]thiazol-6-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid,

(l) 4'-[[2-ethyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

(m) 4'-[[2-n-butyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

(n) 4'-[[2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid,

(o) 4'-[[2-n-propyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

(p) 4'-[[2-n-propyl-4-methyl-6-(imidazo[2,1-b]thiazol-6-yl)-benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

(q) 4'-[(2-n-propyl-4-methyl-6-(1-methyl-6-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid, and

(r) 4'-[(2-ethyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid, and the salts thereof with inorganic or organic acids or bases.

5. 4'-[[2-n-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid and the salts thereof with inorganic or organic acids or bases.

6. 4'-[(2-Ethyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and the salts thereof with inorganic or organic acids or bases.

7. Physiologically acceptable salts of the compounds according to any one of claims 1 to 6 with inorganic or organic acids or bases.

8. Pharmaceutical compositions containing a compound according to any one of claims 1 to 6 or a physiologically acceptable salt according to claim 7 together with an inert carrier or diluent.

9. Use of a compound according to any one of claims 1 to 7 for preparing a pharmaceutical composition with an angiotensin-antagonist activity.

10. Use of a compound according to any one of claims 1 to 6 or a physiologically acceptable salt thereof as an angiotensin-antagonist.

11. Use of a compound according to any one of claims 1 to 6 or a physiologically acceptable salt thereof in the manufacture of a pharmaceutical composition for use as an angiotensin-antagonist.

12. Use of a compound according to any one of claims 1 to 6 or a physiologically acceptable salt thereof for the treatment of hypertension, pulmonary diseases, cardiac insufficiency, ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), diabetic nephropathy, glaucoma, gastrointestinal and bladder diseases or to prevent the progession of cardiac insufficiency after myocardial infarction.

13. Use of a compound according to any one of claims 1 to 6 or a physiologically acceptable salt thereof for the treatment of depression, Alzheimer's disease, Parkinson syndrome, bulimia, disorders of cognitive function as well as other central nervous system disorders.

14. Use of a compound according to any one of claims 1 to 6 or a physiologically acceptable salt thereof in the manufacture of a pharmaceutical composition for use in the treatment of hypertension, pulmonary diseases, cardiac insufficiency, ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), diabetic nephropathy, glaucoma, gastrointestinal and bladder diseases or to prevent the progession of cardiac insufficiency after myocardial infarction.

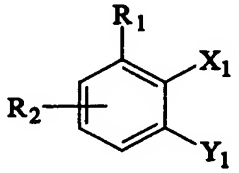
15. Use of a compound according to any one of claims 1 to 6 or a physiologically acceptable salt thereof in the manufacture of a pharmaceutical composition for use in the

treatment of depression, Alzheimer's disease, Parkinson syndrome, bulimia, disorders of cognitive function as well as other central nervous system disorders.

16. Process for preparing a pharmaceutical composition according to claim 8, characterised in that a compound according to any one of claims 1 to 7 is incorporated in an inert carrier or diluent by a non-chemical method.

17. Process for preparing a benzimidazole according to any one of claims 1 to 7, characterised in that

a) a compound of general formula

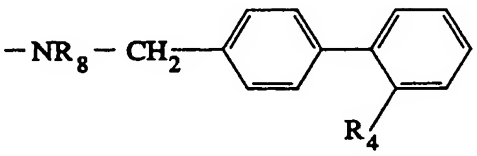


(III)

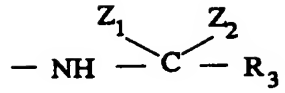
wherein

R_1 and R_2 are defined as in any one of claims 1 to 6,

one of the groups X_1 or Y_1 represents a group of general formula



and the other group X_1 or Y_1 represents a group of the general formula



wherein

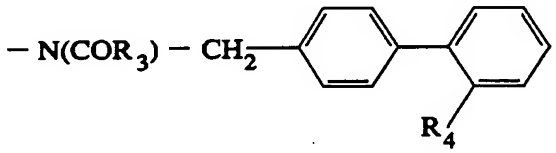
R_2 and R_4 are defined as in any one of claims 1 to 6,

R_8 represents a hydrogen atom or an R_3CO- group, wherein

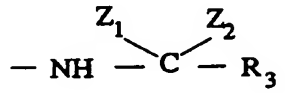
R_3 is as defined in any one of claims 1 to 6,

Z_1 and Z_2, which may be identical or different, represent optionally substituted amino groups or hydroxy or mercapto groups optionally substituted by lower alkyl groups or

Z_1 and Z_2 together represent an oxygen or sulphur atom, an optionally C_{1-3}-alkyl substituted imino group, an alkylenedioxy or alkylenedithio group, each having 2 or 3 carbon atoms, but one of the groups X_1 or Y_1 must represent a group of general formula

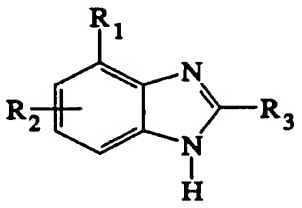


or



is cyclised and a corresponding N-oxide which might thus be obtained is reduced or

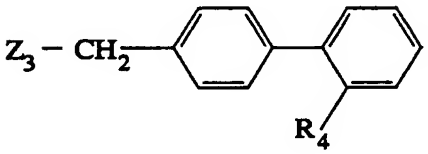
b) a benzimidazole of general formula



(III),

wherein

R_1 to R_3 are as defined in any one of claims 1 to 6, is reacted with a biphenyl compound of general formula



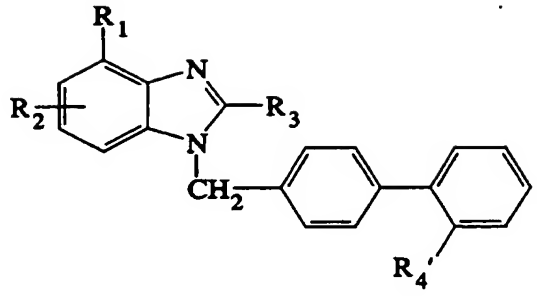
(IV),

wherein

R_4 is as defined in any one of claims 1 to 6 and

Z_3 represents a nucleophilic leaving group, or

c) in order to prepare a compound of general formula I wherein R_4 represents a carboxy group, a compound of general formula

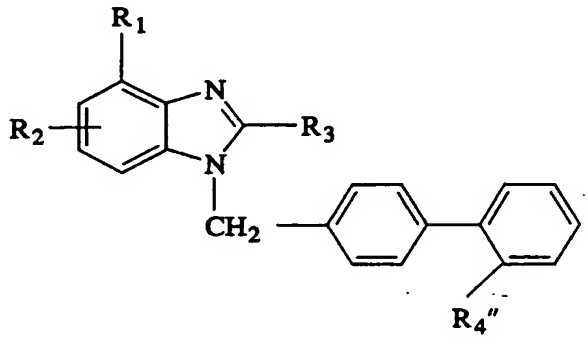


(V),

wherein

R_1 to R_3 are as defined in any one of claims 1 to 6 and R_4' represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis, is converted into a corresponding carboxy compound or

d) in order to prepare a compound of general formula I wherein R_4 represents a 1H-tetrazolyl group, a protecting group is split off from a compound of general formula



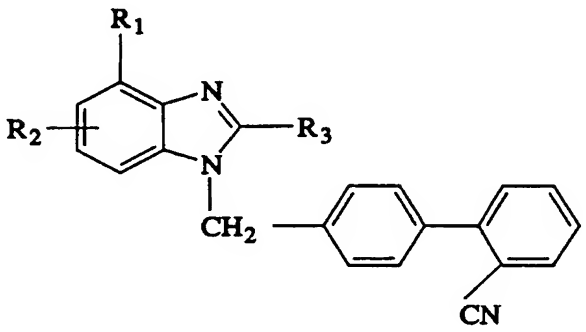
(VI),

wherein

R_1, R_2 and R_3 are defined as hereinbefore and

R_4'' represents a 1H-tetrazolyl group protected in the 1- or 3-position by a protecting group, or

(e) in order to prepare a compound of general formula I wherein R_4 represents a 1H-tetrazolyl group, a compound of general formula

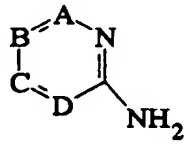


(VII),

wherein

R_1 to R_3 are defined as hereinbefore, is reacted with hydrazoic acid or the salts thereof or

(f) in order to prepare compounds of general formula I wherein R_2 represents one of the imidazo[1,2-a]-pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-c]-pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo-[1,2-b]pyridazin-2-yl or imidazo[2,1-b]thiazol-6-yl groups mentioned hereinbefore, a compound of general formula



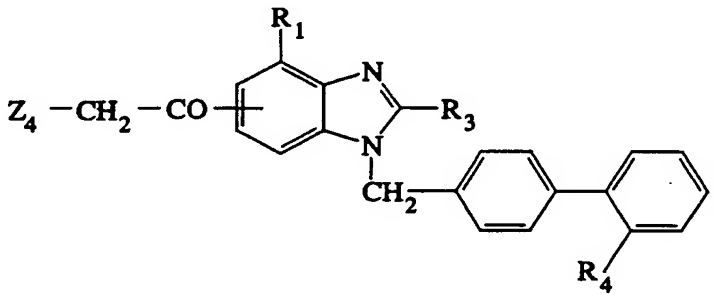
(VIII),

wherein

one of the groups A, B, C or D represents an optionally methyl-substituted methine group or a nitrogen atom and the remaining groups A, B, C or D represent methine groups or

A and B each represent methine and the -C=D- group represents a sulphur atom,

is reacted with a compound of general formula



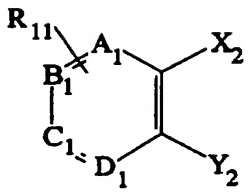
(IX),

wherein

R_1, R_3 and R_4 are as defined in any one of claims 1 to 6 and Z_4 represents a nucleophilic leaving group or

g) in order to prepare compounds of general formula I wherein R_2 represents one of the benzimidazol-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl, imidazo[4,5-d]pyridazin-2-yl or purin-8-yl groups mentioned in any one of claims 1 to 6,

a compound of general formula



(X),

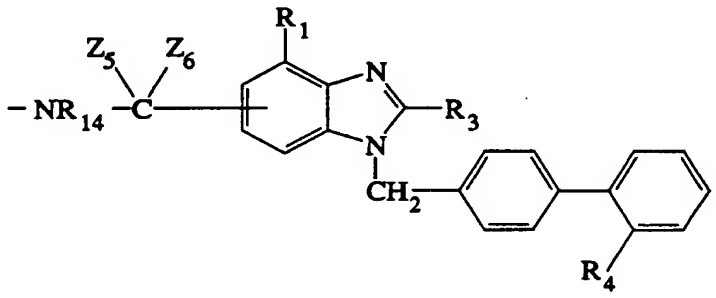
wherein

none, one or two of the groups A_1, B_1, C_1 or D_1 represents a nitrogen atom and

the remaining groups A_1, B_1, C_1 or D_1 represent methine groups,

R_{11} represents a hydrogen or fluorine atom or a methyl or trifluoromethyl group,

one of the groups X_2 or Y_2 represents an R_{13}-NH- group and the other X_2 or Y_2 group represents a group of general formula



wherein

R_1, R_3, and R_4 are as defined in any one of claims 1 to 6, one of the groups R_{13} or R_{14} represents a hydrogen atom and

the other R_{13} or R_{14} group represents a hydrogen atom, a C_{1-6}-alkyl group or a C_{3-7}-cycloalkyl group,

Z_5 and Z_6, which may be identical or different, represent optionally substituted amino groups or hydroxy or mercapto groups optionally substituted by lower alkyl groups or

Z_5 and Z_6 together represent an oxygen or sulphur atom, an optionally C_{1-3}-alkyl-substituted imino group, an alkylenedioxy or alkylenedithio group each having 2 or 3 carbon atoms,

is cyclised and any corresponding N-oxide which is thus obtained is reduced and a compound thus obtained is subsequently hydrolysed, if required, and

if necessary a protecting group used during the reactions a) to g) in order to protect reactive groups is cleaved and

if required, an isomer mixture thus obtained is resolved into its isomers, and

if required a compound of general formula I thus obtained is converted into a salt thereof.

18. A process according to claim 17 which includes the step of converting an obtained compound of formula I into a physiologically acceptable salt thereof.

19. A process according to claim 17(f) or 18 wherein Z_4 represents a chlorine or bromine atom.

20. A commercial package containing, as active ingredient, a compound according to any one of claims 1 to 6,

or a physiologically acceptable salt thereof, together with instructions for its use for the treatment of hypertension, pulmonary diseases, cardiac insufficiency, ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), diabetic nephropathy, glaucoma, gastrointestinal and bladder diseases or to prevent the progression of cardiac insufficiency after myocardial infarction.

21. A commercial package containing, as active ingredient, a compound according to any one of claims 1 to 6, or a physiologically acceptable salt thereof, together with instructions for its use for the treatment of depression, Alzheimer's disease, Parkinson syndrome, bulimia, disorders of cognitive function as well as other central nervous system disorders.

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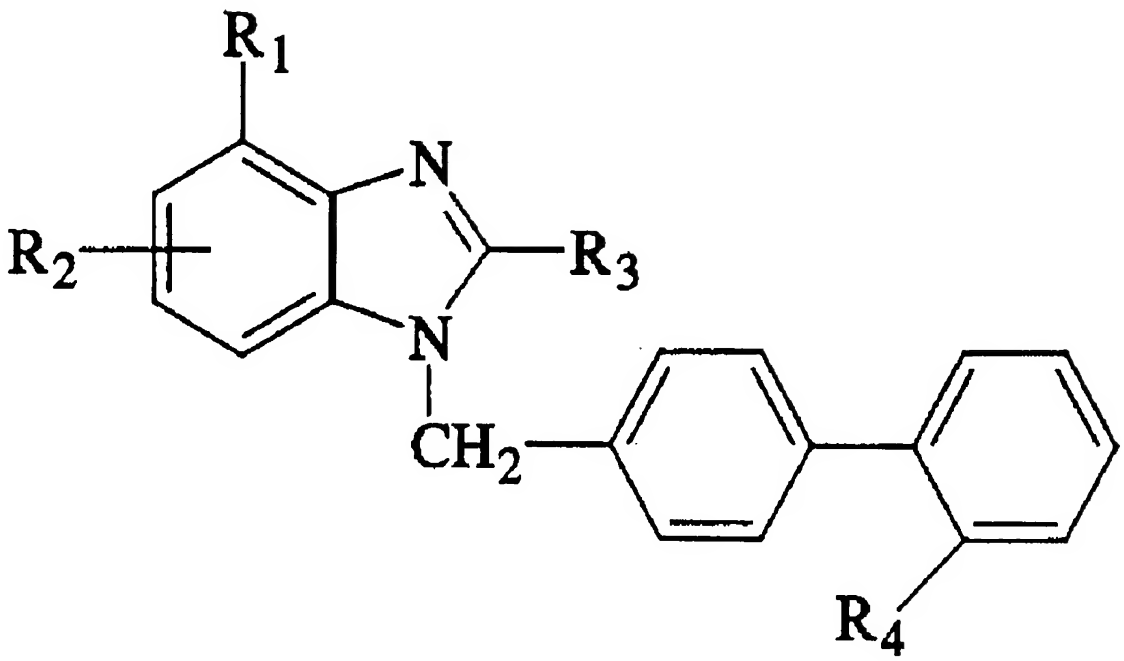
OTTAWA, CANADA

PATENT AGENTS

C



(I)